REMARKS

Claims 1, 2, 5-10, and 12-18 are pending. Claims 8, 10, and 12-18 stand withdrawn as being drawn to non-elected subject matter. Applicants have cancelled claims 2 and 5 without prejudice and added new claims 19-42. Claims 1, 6-10, 12-43 will therefore be pending upon entry of the proposed amendments.

Amendments to claim 1

Applicants have incorporated the limitations of claim 5 (now cancelled). As such, claim 1 as presently amended now requires that R^3 must be $-NHC(O)R^{10}$ or $-C(O)NR^{11}R^{12}$. Claim 1 as presently amended also requires that m must be 0 or 1; n must be 0; and t must be 0 or 1. Support for these amendments can be found throughout the specification, e.g., at page 5, line 2; page 9, line 2; and page 18, line 26.

New Claims 19-21

New claim 19, which depends from claim 1, is directed to compounds in which R^1 is halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

New claim 20, which depends from claim 1, is directed to compounds in which R^1 is fluoro, chloro, methyl, or trifluoromethyl.

New claim 21, which depends from claim 1, is directed to compounds in which R^1 is chloro.

Support for new claims 19-21 can be found throughout the specification, e.g., at page 5, lines 10-14.

New Claims 22-23

New claim 22, which depends from claim 1, is directed to compounds in which R^9 is halogen, hydroxyl, carboxyl, methyl, methoxy, methoxycarbonyl or trifluoromethyl.

New claim 23, which depends from claim 1, is directed to compounds in which R^9 is halogen or hydroxyl.

New Claims 24-26

New claim 24, which depends from claim 1, is directed to compounds in which R^{10} is a group C_1-C_6 alkyl, C_3-C_6 cycloalkyl or phenyl, each of which may be optionally substituted by one or two substituents independently selected from halogen, C_1-C_6 alkyl and C_1-C_6 alkoxy.

New claim 25, which depends from claim 1, is directed to compounds in which R^{10} is C_1-C_6 alkyl, which may be optionally substituted by one or two substituents independently selected from halogen, C_1-C_6 alkyl and C_1-C_6 alkyl.

New claim 26, which depends from claim 1, is directed to compounds in which R^{10} is unsubstituted C_1-C_6 alkyl.

Support for new claims 24-26 can be found throughout the specification, e.g., at page 11, lines 4-10.

New Claims 27-28

New claim 27, which depends from claim 1, is directed to compounds in which R^{11} and R^{12} are each independently, hydrogen or a C_1-C_6 alkyl group optionally substituted by a substituent selected from amino, hydroxyl, C_1-C_4 alkoxy, C_1-C_2 alkoxycarbonyl, C_1-C_2 alkylcarbonylamino and a 3- to 6-membered saturated or unsaturated ring optionally comprising one or two ring heteroatoms selected from nitrogen and oxygen and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent independently selected from oxo and C_1-C_2 alkyl.

New claim 28, which depends from claim 1, is directed to compounds in which R^{11} and R^{12} are each independently, hydrogen or an unsubstituted C_1-C_6 alkyl group.

Support for new claims 27 and 28 can be found throughout the specification, e.g., at page 13, lines 24 through page 14, line 26; and page 16, line 8 through page 17, line 2.

New Claims 29-38

New claim 29, which depends from claim 1, is directed to compounds in which:

- m is 1;
- R^{10} is a group C_1-C_6 alkyl, C_3-C_6 cycloalkyl or phenyl, each of which may be optionally substituted by one or two substituents independently selected from halogen, C_1-C_6, preferably C_1-C_4, alkyl and C_1-C_6, preferably C_1-C_4, alkoxy; and
- R^{11} and R^{12} are each independently, hydrogen or a C_1-C_6 alkyl group optionally substituted by a substituent selected from amino, hydroxyl, C_1-C_4 alkoxy, C_1-C_2 alkoxycarbonyl, C_1-C_2 alkylcarbonylamino and a 3- to 6-membered saturated or unsaturated ring optionally comprising one or two ring heteroatoms selected from nitrogen and oxygen and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent independently selected from oxo and C_1-C_2 alkyl.

Support for new claim 29 can be found throughout the specification, e.g., at page 11, lines 4-7; page 16, line 23 through page 17, line 2; and page 18, line 21 through page 19, line 3.

New claims 30, 32, and 33, each of which depend from claim 29, recite the R^1 definitions that are set forth in new claims 19, 20, and 21, respectively. New claim 31, which depends from claim 29, is directed to compounds in which R^1 is halogen.

New claims 34 and 35, each of which depends from claim 29 or 32, recite the R^9 definitions that are set forth in new claims 22 and 23, respectively.

New claim 36, which depends from claim 29 or 32, recites the R^{10} definition that is set forth in new claim 25. New claim 37, which depends from claim 36, recites the R^{10} definition that is set forth in new claim 26.

New claim 38, which depends from claim 29 or 32, recites the R^{11}/R^{12} definition that is set forth in new claim 28.

New Claims 39-42

New claim 39, which depends from claim 29 or 32, is directed to compounds in which:

R^9 is halogen, hydroxyl, carboxyl, methyl, methoxy, methoxycarbonyl or trifluoromethyl;

R^{10} is C_1-C_6 alkyl, which may be optionally substituted by one or two substituents independently selected from halogen, C_1-C_6 alkyl and C_1-C_6 alkoxy; and

R^{11} and R^{12} are each independently, hydrogen or an unsubstituted C_1-C_6 alkyl group.

Support for new claim 39 can be found throughout the specification, e.g., at page 9, lines 18-19; page 11, lines 4-10; page 16, line 23 through page 17, line 2; and page 18, line 21 through page 19, line 3.

New claim 40, which depends from claim 39, recites the R^9 definition that is set forth in new claims 23. New claim 41, which depends from claim 39, recites the R^{10} definition that is set forth in new claims 26. New claim 42, which depends from claim 39, recites the R^9 definition that is set forth in new claims 23and the R^{10} definition that is set forth in new claims 26.

No new matter is introduced by these amendments.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 5, 6, and 9 remain rejected for allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. According to the Office: "the specification, while being enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents" (Office Action, page 13).

The rejection, which spans pages 2-7 and 13-32 of the Office Action, is very detailed and includes a number and variety of supporting information, such as quotations from a recent treatise on organic synthesis, case law citations, as well as the results of a search of the Aldrich Chemical Company catalog. The rejection appears to focus on the following three issues:

1. Number and nature of exemplified compounds.
2. Predictability.
3. Availability of starting materials to make the claimed compounds.

[A] With regard to item (1), the Office states, in part (see pages 3, 4, and 5 of the Office Action; bold emphasis in original; underline emphasis added):

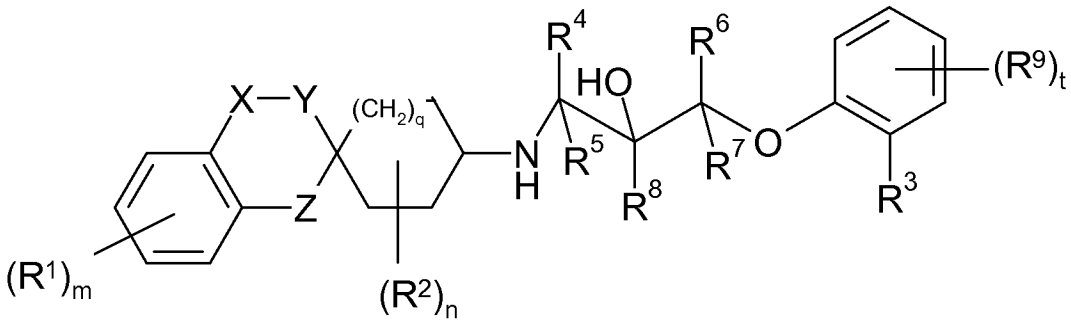
> [T]he paucity of working examples point to the key deficit in the disclosure, namely that undue experimentation would be required to practice the invention and that the 'how to use' requirement has not been met. …
>
> **Only five actual compounds are described in the specification**. Most of the groups recited in the instant claims are entirely prophetic. …
>
> While the examiner can do very little to reject small, modest changes such as the addition of a methyl group or halogen, the instant claims recite substituents that go far beyond even specious reasoning. For example in claim 1, the following is a recitation for a group: … <u>The only example is methyl. It appears that based upon the arguments of counsel defending such a claim that all of these groups are obvious over each other</u>. …
>
> <u>In this case the claims bear no structural resemblance to the exemplified compounds, which are relatively homogenous and non-representative of the scope claimed</u>. In order to practice the full scope of the invention, one of ordinary skill would not only need to create synthetic procedures *de novo*, but also decide what compounds to prepare. <u>The specification gives literally no guidance to what the requirements for activity are i.e. which substituents would be preferred</u>.

Applicants respectfully disagree.

[1] Applicants first wish to address the Office's statement "[i]t appears that based upon the arguments of counsel defending such a claim that all of these groups are obvious over each other" (Office Action, page 4). Applicants did not in any way make such a representation or argument. Rather, Applicants argued that a person of ordinary skill in the art, using the knowledge he or she has, using the tools of chemistry, and guided by the Specification, could make the claimed compounds without undue experimentation.

[2] <u>The Claimed Compounds</u>

[a] Claim 1 is directed to compounds having formula (I):



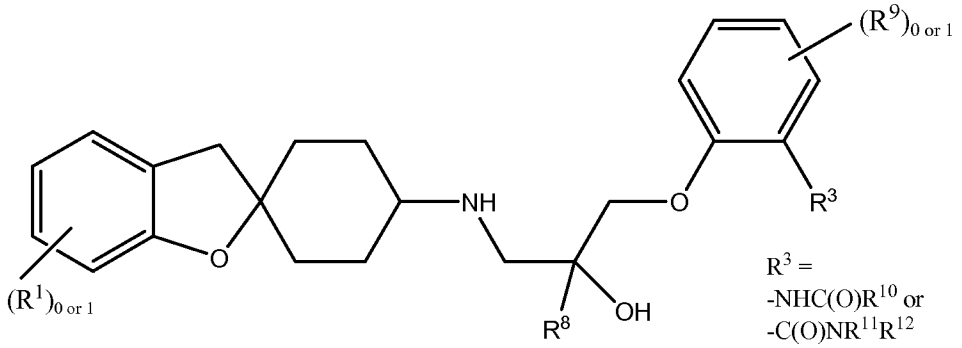
(I).

The claims in their previously presented form already required that X must be a bond, Y must be -O-, Z must be $-CH_2$; q must be 1; and R^4, R^5, R^6, R^7 must each be a hydrogen atom.

The claims as presently amended now further require:

- R^3 must either be $-NHC(O)R^{10}$ or $-C(O)NR^{11}R^{12}$;
- m must be 0 or 1 (i.e., the leftmost phenyl ring in formula (I) must either be unsubstituted or monosubstituted;
- n must now be 0 (so R^2 must now be absent); and
- t must be 0 or 1.

[b] As such, the claimed compounds are required to have the following core structure, which is referred to throughout as formula (A):



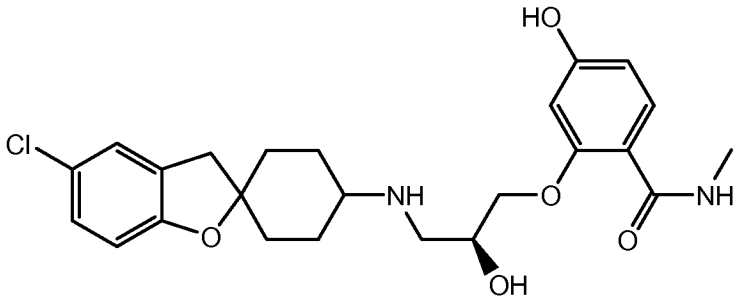
R^3 =
-NHC(O)R^{10} or
-C(O)N$R^{11}R^{12}$

R^1 =
halogen,
cyano,
hydroxyl,
C_1-C_6 alkyl,
C_1-C_6 haloalkyl,
C_1-C_6 alkoxy or
sulphonamido

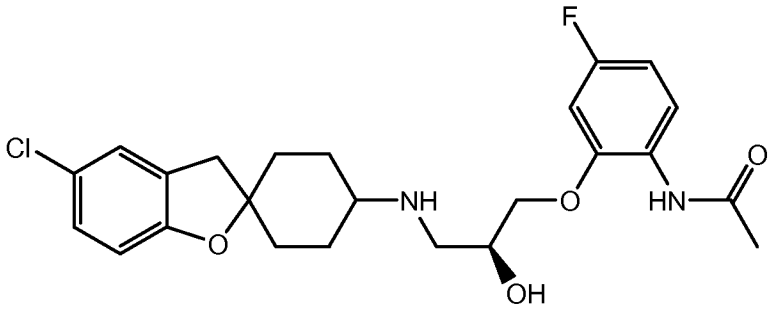
R^8 =
hydrogen or
C_1-C_6 alkyl

R^9 =
halogen,
cyano, hydroxyl,
carboxyl, C_1-C_6 alkoxy,
C_1-C_6 alkoxycarbonyl,
C_1-C_6 haloalkyl, or
C_1-C_6 alkyl optionally substituted by at least one substituent selected from carboxyl and C_1-C_6 alkoxycarbonyl

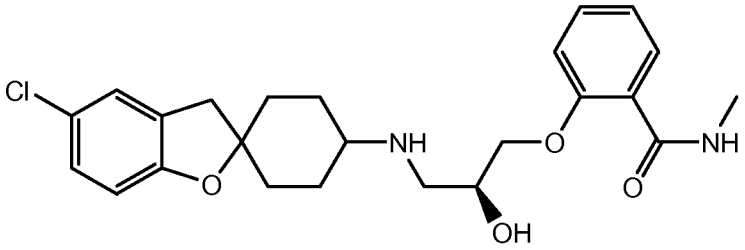
[c] Applicants respectfully disagree with the Office's statement "[i]n this case the claims bear no structural resemblance to the exemplified compounds, which are relatively homogenous and non-representative of the scope claimed" (Office Action, page 5). The chemical structures of the compounds exemplified in the specification are shown below:



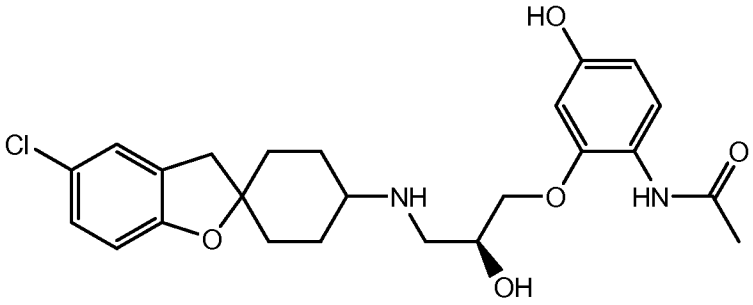
Example 1



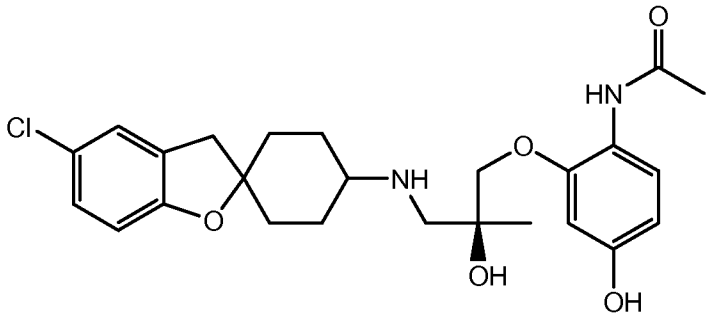
Example 2



Example 3



Example 4



Example 5

Claim 1 is directed to compounds having a very specific core structure. In other words, claim 1 precludes variability within the constituent atoms that make up this very specific core structure. Looking no further than this, it is readily apparent that the claims do in fact bear significant "structural resemblance" to the exemplified compounds. Claim 1 does allow for variability within the substituents that are attached to the core structure, but even where variability is permitted, the substitution pattern present on the exemplified compounds is representative of the claimed genus. By way of example, R^3 must now be either an amide (i.e., $-C(O)NR^{11}R^{12}$) or a reverse amide ($-NHC(O)R^{10}$) group. As can be seen, the specification teaches compounds in which the R^3 groupis an amide as well as compounds in which the R^3 group is a reverse amide. New claims 24-29, 36, 37, 38, 39, 41, and 42, which are offered for the Office's consideration in the present reply, recite amended definitions of sub-variables R^{10}, R^{11}, and R^{12}.

[d] The specification teaches, for example, that the claimed compounds have activity as modulators of chemokine receptor (especially MIP-1α chemokine receptor) activity (page 22, line 27 through page 23, line 2):

> The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially MIP-1α chemokine receptor) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS).

As further evidence of this, Applicants provide biological data that was obtained by testing the compounds exemplified in the specification (see Table 1 below[1]). More specifically, the data shows the IC_{50} values exhibited by each of the exemplified compounds in the assay described on page 40 of the specification. As can be seen, the exemplified compounds exhibited IC_{50} values in the sub-micromolar range.

[1] This data is not disclosed in the specification as filed.

Table 1

Example No.	IC_{50} (μM)
1	0.16
2	0.023
3	0.23
4	0.032
5	0.061

[e] Finally, Applicants wish to address the Office's statement "[t]he specification gives literally no guidance to what the requirements for activity are i.e. which substituents would be preferred" (Office Action, page 5). Applicants respectfully disagree and submit that the specification provides ample guidance along these lines. For example, the specification provides a fairly extensive roadmap of preferred compound attributes (see pages 5-19) and well as example specific formula (I) compounds (*supra*).

The above-quoted statement suggests that in order to practice the claimed invention, one must have a somewhat precise understanding as to how the invention works. Such a standard is improper and is not even required of the inventors themselves. A person of ordinary skill in the art can ascertain, without undue experimentation, whether a particular compound of the claims may be suitable, e.g., for treating a particular disorder. E.g., he or she can subject the compound to one of the assays disclosed in the Specification or some other art-recognized assay.

[B] Applicants now turn to item (2) on page 18 of the present reply.

[1] The Office states "[c]hemistry is unpredictable" (Office Action, page 14). The Office Action then goes on to quote a passage from a treatise related to organic synthesis. The passage that is quoted by the Office begins with "[m]ost non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are" (Office Action, page 14).

Applicants, however, are not claiming organic compounds, generally, nor are they claiming methods of making or using organic compounds, generally. Rather, Applicants are claiming a narrow, well defined genus of compounds. Further, as taught in the specification, Applicants have successfully synthesized five representative compounds of this genus using the methodology taught in the specification. The skilled artisan would therefore reasonably expect that this methodology (or modifications thereof) could be used to prepare Applicants' non-disclosed variants as well. In any event, and as discussed in the previous reply, to enable a claim to a genus, one need **not** disclose and test every species encompassed by the genus, **even in the so-called unpredictable arts**. To require as such would limit the Applicants merely to what he or she has already done. Again, this is not the law. *See, e.g., In re Angstadt*, 190 USPQ 214, (CCPA 1976). See also MPEP § 2164.02: "[b]ut because only an enabling disclosure is required, applicant need not describe all actual embodiments."

Finally, while some level of unpredictability can be associated with chemical reactions, the Office has provided no specific evidence as to why the unpredictability of chemical reactions would prohibit their use in making Applicants' non-disclosed compounds. By way of example, the specification teaches a process for installing an amide or reverse amide (i.e., the substituent corresponding to R^3) on the right most phenyl ring in formulas (I) and (A) (see specification at page 20, line 9 through page 21, line 12). Specific examples of this process are provided in Examples 1-5 in the specification. The Office not address, for example, what it is about the synthesis of Applicants' contemplated, but nondisclosed, amides or reverse amides that would require undue experimentation. The Office asserts that "[i]n order to practice the full scope of

the invention," the skilled artisan would "need to create synthetic procedures *de novo*" (Office Action, page 5). However, as discussed in Applicants' previous reply, the enablement inquiry does not turn on whether experimentation may be needed to practice the claimed invention. Rather, the enablement inquiry turns on whether the amount of experimentation needed to practice the claimed invention is undue. *See, e.g., In re Angstadt and Griffin*, 190 USPQ 219 ("The key word is 'undue' and not 'experimentation.'").

In conclusion, a person of ordinary skill in the art, given his or her knowledge of the prior art and the ability to modestly experiment, could bridge any gaps between the breadth of the disclosure and the breadth of the claims.

[2] The Office (Office Action, pages 28-32) discusses four references which describe inactive compounds.

Xie et al. "Identification of novel series of human CCR1 antagonists." *Bioorganic & Medicinal Chemistry Letters* **2007**, doi: 10.1016/j. bmcl. 2007.09.068 ("Xie");

Ting et al. "The synthesis of substituted bipiperidine amide compounds as CCR3 ligands: Antagonists versus agonists." *Bioorganic & Medicinal Chemistry Letters* **2005** 15, 3020-3023 ("Ting");

Thoma et al. "Orally Bioavailable Competitive CCR5 Antagonists." *Journal of Medicinal Chemistry* **2004**, *47*, 1939-1955 ("Thoma") all describe bi-piperidinyl compounds; and

Brown et al. "Novel CCR1 antagonists with improved metabolic stability." *Bioorganic & Medicinal Chemistry Letters* **2004**, *14*, 2175-2179 ("Brown").

The Office Action states, in part (pages 28 and 31):

> Regardless, structural requirements for chemokine binding to CCR1, CCR3, and CCR5 are stringent as is well known in the art. These compounds are sensitive to structural changes that may be relatively minor in the chemical sense, …Thus it is clear that substitution can have a very pronounced impact on the active pharmacophore, and a choice of the wrong substituent or too many substituents gives compounds with no activity.

[a] Applicants first wish to briefly comment on the chemical structures of the compounds disclosed in the above-mentioned references.

First, Xie et al. "Identification of novel series of human CCR1 antagonists." *Bioorganic & Medicinal Chemistry Letters* **2007**, doi: 10.1016/j. bmcl. 2007.09.068 ("Xie"), Ting et al. "The synthesis of substituted bipiperidine amide compounds as CCR3 ligands: Antagonists versus agonists." *Bioorganic & Medicinal Chemistry Letters* **2005** 15, 3020-3023 ("Ting"), and Thoma et al. "Orally Bioavailable Competitive CCR5 Antagonists." *Journal of Medicinal Chemistry* **2004**, *47*, 1939-1955 ("Thoma") all describe bi-piperidinyl compounds.

Second, Brown et al. "Novel CCR1 antagonists with improved metabolic stability." *Bioorganic & Medicinal Chemistry Letters* **2004**, *14*, 2175-2179 ("Brown") describes compounds which all have a quinoxaline core.

In contrast, Applicant's compounds do not have a bi-piperidinyl nor a quinoxaline as the core structure, but rather the spiro-fused ring containing core structure recited in claim 1. There is no connection between the structure-activity relationship (SAR) of compounds of Xie, Ting, Thoma or Brown with the SAR of compounds of Applicant's claim 1. Therefore, the results reported by Xie, Ting, Thoma and Brown could not be reasonably be transferred to directly apply to the compounds of the present application.

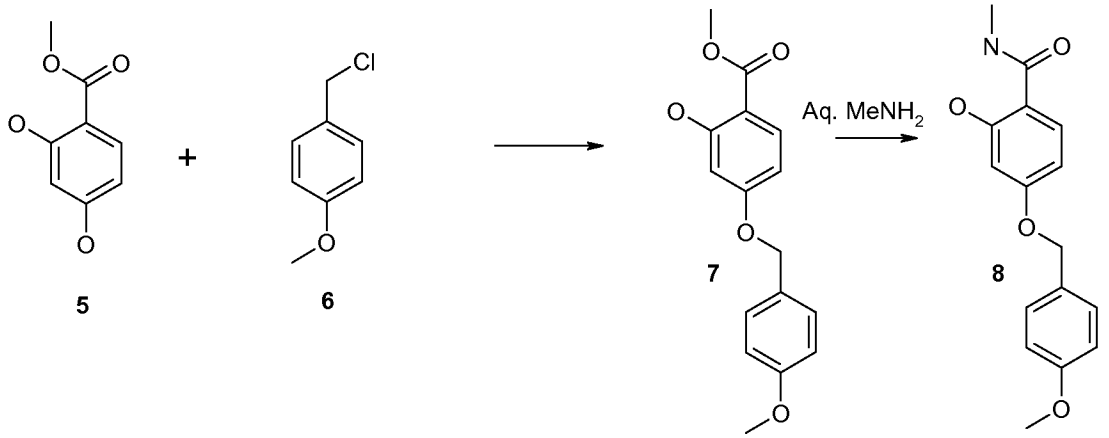
[b] In addition, Applicants have demonstrated that predictability of the claimed compounds is high. As discussed in paragraph **[A][2][d]** of the present reply, the exemplified compounds exhibited IC_{50} values in the sub-micromolar range when screened in the assay described on page 40 of the specification. A person of ordinary skill in the art would therefore reasonably expect Applicants' nondisclosed variants to have this activity as well. That being said, even if one or more of the claimed compounds were found to be inactive (and Applicants do not concede that this is the case here), that does not render the claims unpatentable. The claims need not exclude inoperative embodiments. As the Federal Circuit explained in *Atlas Powder Co. v. E. I. Du Pont De Nemours & Co.* 224 USPQ 409 (Fed. Cir. 1984):

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the

claims to specifically exclude … possible inoperative substances…" *Atlas Powder* at 414.

[C] Applicants now turn to item (3) on page 18 of the present reply.

[1] Applicants believe, after reviewing the synthesis scheme on page 16 of the Office Action, that compounds **5**, **6**, **7**, and **8** in that scheme should have the following structures :



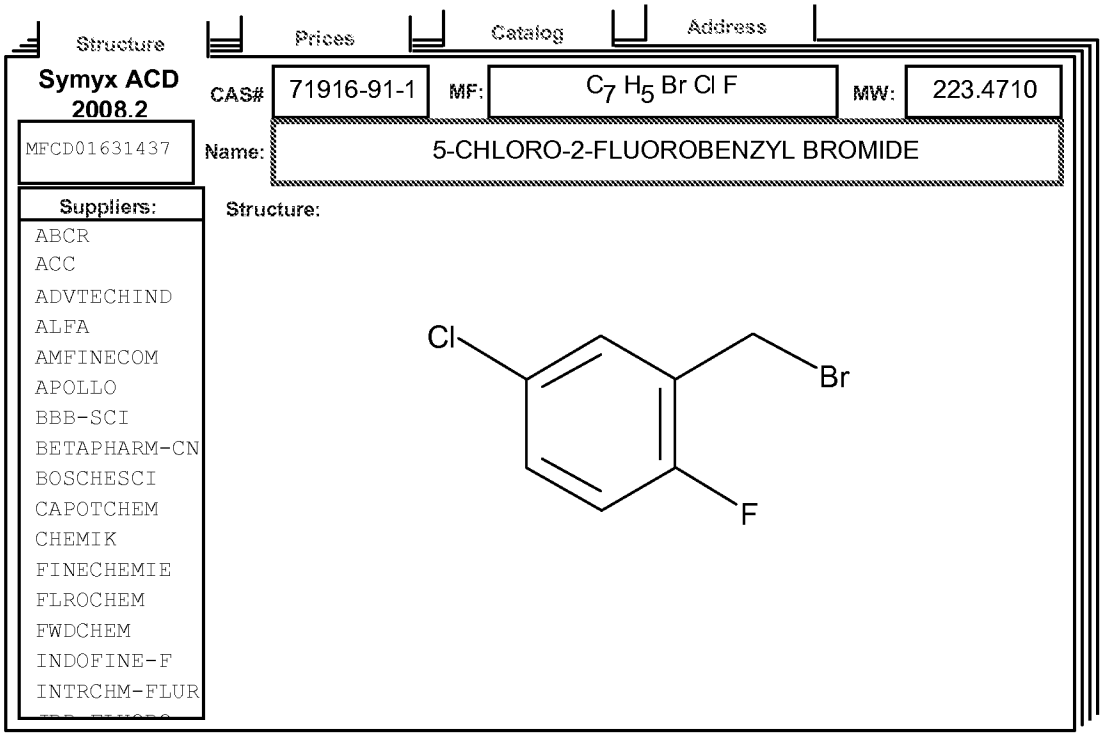
Compounds **5** and **6** above are commercially available. Compounds **7** and **8** above can be prepared as described in steps 1 and 2, respectively in Example 1 (specification at page 28, line21 though page 29, line 18.

[2] The Office indicates that it conducted a search to determine whether some of Applicants' starting materials and intermediates were commercially available. Applicants respectfully disagree that the Office's search weighs on the side of a finding of a non-enabling disclosure. This is discussed in more detail below.

[a] First, there is no legal requirement (or requirement in the specification or claims) that the claimed compounds must be made from commercially available starting materials.

[b] Second, the Office's search was limited to only **one** vendor (Aldrich). The fact that the compound in question was not available from Aldrich would not have led the skilled artisan to reasonably conclude that the compound was not commercially available (or otherwise unavailable by other means, such as conventional organic synthesis).

[c] Third, compounds **1**, **2**, and **9** in the synthesis scheme on page 16 of the Office Action are commercially available (the Office is respectfully directed to the following three screen shots):



Structure | Prices | Catalog | Address

Symyx ACD 2008.2

MFCD00798168

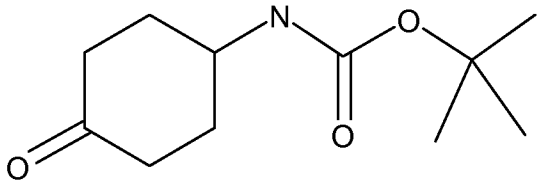
CAS# 179321-49-4 MF: $C_{11}H_{19}NO_3$ MW: 213.2750

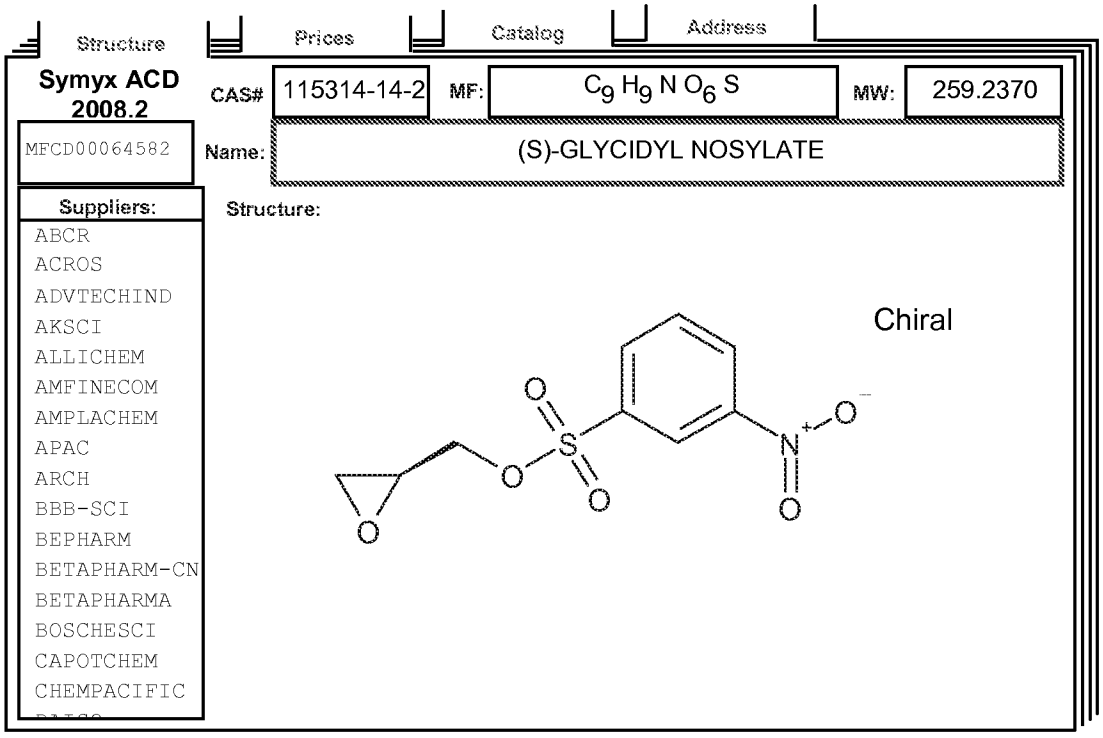
Name: N-4-BOC-AMINOCYCLOHEXANONE

Suppliers:

AALENCHEM
AATPHARM
ABCHEM-INC
ABCR
ACC
ACCELEDEV
ADVTECHIND
ALLICHEM
AMFINECOM
AMPLACHEM
ANDACHEM
APAC
APOLLO-INTER
ASTATECH
ASTGINC
ATOMOLE

Structure:





[d] The specification does disclose that the starting materials and other reagents were, as of Applicants' filing date, "commercially available, known in the literature, or may be prepared using known techniques" (specification at page 22, lines 2-3). In addition, detailed synthesis information (solvents, reagents, reaction temperatures, use of protecting groups) for the process steps is also provided. See specification at page 21, line 17 through page 22, line 3. The fact that the specification does not disclose such known (and arguably well known) methods and materials does **not** make Applicants' disclosure non-enabling. *See S3 Inc. v. nVIDIA Corp.* 59 USPQ2d 1745, 1749-50, (2001):

> ('[P]atents are written by and for skilled artisans'). To hold otherwise would require every patent document to include a technical treatise for the unskilled reader.

In summary, a person of ordinary skill in the art, using the knowledge he or she has, using the tools of chemistry, and guided by the Specification, could make the claimed compounds without undue experimentation.

In view of the foregoing, Applicants respectfully request that the 35 U.S.C. § 112, first paragraph rejection be reconsidered and withdrawn.

Rejections on the ground of nonstatutory obviousness-type double patenting

Claims 1-2, 5-7, and 9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 and 10 of USSN 10/579,545 "in view of Xue et al. U.S. Pre-Grant Publication 2006/0252751" (Office Action, page 5).

Claims 1-2, 5-7, and 9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 and 12 of USSN 10/581,171 "in view of Xue et al. U.S. Pre-Grant Publication 2006/0252751" (Office Action, page 9).

Claims 1-2, 5-7, and 9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12, and 14 of USSN 10/583,468 "in view of Xue et al. U.S. Pre-Grant Publication 2006/0252751" (Office Action, page 9).

Claims 1-2, 5-7, and 9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 13 of USSN 10/520,699 "in view of Xue et al. U.S. Pre-Grant Publication 2006/0252751" (Office Action, pages 9-10).

According to the Office (Office Action, page 11, emphasis added):

> It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare the compounds of the instant case. The compounds of the claims at hand are analogs of old compounds. One of ordinary skill would have been motivated to make the compounds of the invention because **he would expect the compounds to have similar properties, indeed we see that these compounds have the same properties**.

Applicants respectfully disagree with the grounds for the rejection and request that the rejection be reconsidered and withdrawn for any of the following independent reasons.

[A] The Office states:

> One of ordinary skill would have been motivated to make the compounds of the invention because **he would expect the compounds to have similar properties, indeed we see that these compounds have the same properties**.

The Federal Circuit discussed obviousness rejections in *In re Dillon* 16 USPQ2d 1897, 1919-1920 (1990, emphasis in original):

> The factual determination of the scope and content of the prior art, *see Graham*, 383 U.S. at 17, 148 USPQ at 467, is, of course directed to prior art that meets the conditions of section 102. Section 102 describes prior art as what is published or otherwise known, including subject matter in public use or on sale. Not included is what is unknown, or knowledge that became known to the inventor through the inventor's own research:
>
> > To rely on an equivalence *known only to the applicant* to establish obviousness is to assume that his disclosure is a part of the prior art. The mere statement of this proposition reveals its fallaciousness. *[citation omitted]*

The Office states "indeed we see that these compounds have the same properties" (Office Action, page 11). However, the claimed compounds and their properties are only taught in the present specification, and not in the prior art of record. The Office cannot rely on equivalence known only to Applicants, because as discussed above, Applicants' specification is not (and cannot be) part of the prior art in an obvious rejection. The rejection should therefore be

withdrawn because it is improper for the Office to use Applicants' own discovery as the basis for an obvious rejection.

[B]

[1] It is well settled that the obviousness-type double patenting analysis must focus only on what is **claimed** in the reference patent. See, e.g., MPEP § 804 (emphasis added):

> <In determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is - does any claim in the application define an invention that is >anticipated by, or is< merely an obvious variation of >,< an invention **claimed** in the patent? …
>
> A double patenting rejection of the obviousness-type>, if not based on an anticipation rationale,< is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). **Therefore, *>the< analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination**. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). …

[2] The Federal Circuit discussed the requirements for establishing a *prima facie* case of obviousness for a claimed chemical compound in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd*. 492 F.3d 1350, 135x (emphasis added):

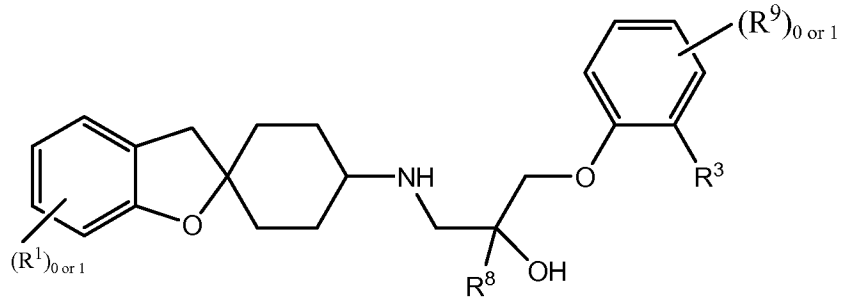
> Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon*, 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed.Cir.1985).
>
> We elaborated on this requirement in the case of *In re Deuel*, 51 F.3d 1552, 1558 (Fed.Cir.1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new

compounds." *Id*. A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id*. We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id*. (citing *In re Jones*, 958 F.2d 347 (Fed.Cir.1992); *Dillon*, 919 F.2d 688;*Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed.Cir.1984)).

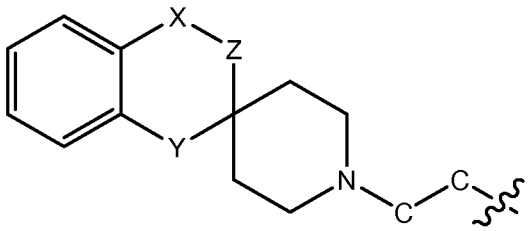
[5] That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[2] While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, **the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination**. *KSR*, 127 S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id*. **Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound**.

[3] Thus, the Office must provide some reason why the claimed compounds would have been obvious over the claims of each of the cited U.S. patent application publication in view of Xue. More specifically, the Office must provide some reason why a chemist would have modified the reference claims in view of the teachings of Xue.

[4] The present claims are directed to compounds having the following formula:



[5] The claims in the four reference patent applications cited by the Office are each directed to compounds that include as part of their chemical structure the following spiro-fused, piperidinyl-containing fragment:

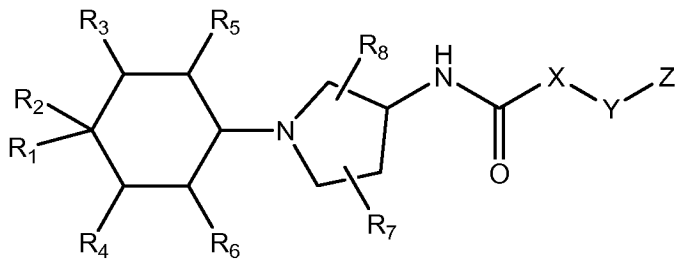


.

The piperidinyl nitrogen is in turn attached to a carbon-containing, acyclic chain.

The modifications needed to arrive at the claimed compounds from those encompassed by the reference claims are precluded by (and therefore not even encompassed by) the claims in each of the foregoing reference applications.

[6] Xue discloses compounds having the following general formula:



Xue discloses that R_1 and R_2 together can form a spirocycle (Xue, page 4, paragraph **[0032]**). The Xue compounds differ from the claimed compounds in at least two ways. First, the leftmost (potentially spiro-fused) ring in the Xue compounds (i.e., the ring in the Xue general formula that bears R_1-R_6) is solely angular in orientation, while the spiro-fused ring in the claimed compounds is linear in orientation. Further, the Xue compounds contain a carbonyl in the sidechain that is attached to this leftmost (potentially spiro-fused) ring. No carbonyls are present in the chain connecting the spiro-fused ring and the rightmost phenyl ring in the claimed compounds.

[7] To arrive at the claimed compounds from those encompassed by the reference claims, one would, at the very least, need to (**i**) replace the piperidinyl nitrogen atom with a carbon atom; and (**ii**) replace the carbon atom (which is in a chain) that is immediately attached to the piperidinyl nitrogen atom with a nitrogen atom. As mentioned above, there is nothing in the reference claims that would have led one to do this: these modifications are precluded by (and therefore not even encompassed by) the reference claims in each of the foregoing reference applications. There is nothing in Xue that would have led one to do this either. Put simply, Xue tells one that the nitrogen atom that is directly attached to the leftmost (potentially spiro-fused) ring must be confined within a five-membered ring and not in chain. There is nothing in Xue that would have led one to ignore this teaching (or ignore Xue's teaching to incorporate carbonyls for that matter either).

At most then, the Office has merely identified some structural elements of the claimed compounds in two different references, in particular two references that each describe two very different scaffolds. However, the Office provides no reason as to why one would have combined these references in the manner needed to arrive at the claimed compounds (i.e., why one would have incorporated certain features, but ignored others that are required by the references). In view of the foregoing, Applicants respectfully request that the rejection be withdrawn.

The fee in the amount of $1,110 for the three month extension of time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No.: 06275-503US1.

Respectfully submitted,

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